COVID-19-associated risks and effects in myasthenia gravis (CARE-MG)

During the COVID-19 pandemic, patients with neuromuscular disorders, especially patients with autoimmune myasthenia gravis, might be at greater risk of worse outcomes than otherwise healthy people because of an immunocompromised state related to immunotherapy and possible respiratory and bulbar muscular weakness. However, cessation of immunotherapy in neuroinflammatory disorders has severe risks as well.[1] Moreover, infections are a well recognised trigger of symptom exacerbation in patients with myasthenia gravis, and some drugs used in therapeutic trials early in the pandemic, including hydroxychloroquine[2] and azithromycin,[3] can provoke symptom exacerbations.

As there was no real-world evidence available at the onset of this pandemic and heightened concern existed for possible misinformation, an international group of neuromuscular physicians developed initial guidelines for managing myasthenia gravis, which were based on previous experience with viral illnesses in this patient population.[4] However, the need for data to answer key clinical questions was quickly recognised and a registry was created to capture high-quality information about outcomes for patients with myasthenia gravis and laboratory-confirmed, or clinically suspected, COVID-19. This physician-reported registry, COVID-19 Associated Risks and Effects in Myasthenia Gravis (CARE-MG), is a joint effort of the International MG/COVID-19 Working Group and neurologists who help to take care of patients with myasthenia gravis globally and was formally launched on April 9, 2020. Registry data elements, inclusion and exclusion criteria, and research study approval are available in the appendix (appendix pp 7–8). The registry is still open and active accrual continues through electronic-form or paper-form submission of case reports. Data entry for each case submission takes approximately 10 min. Additional study details and steps for case submission are available from the Myasthenia Gravis Foundation of America website.[6]

See Online for appendix

A total of 91 patients with myasthenia gravis were included at the time of interim analysis (Oct 5, 2020; appendix pp 10–12). Myasthenia gravis worsening or crisis requiring rescue therapy (eg, intravenous immunoglobulin, plasma exchange, or steroids) in the setting of COVID-19 was reported in 36 (40%) of 91 patients. Complete recovery or discharge to home was reported in 39 (43%) patients, whereas 22 (24%) patients died due to COVID-19.

These preliminary data suggest that a global, physician-reported registry is feasible during times of crisis, even for rare diseases, such as myasthenia gravis. Current data, which might be biased toward poor outcomes reporting, show that patients with myasthenia gravis who are infected with severe acute respiratory syndrome coronavirus 2 are frequently admitted to hospital, have disease exacerbations, and have a higher mortality than the general population with COVID-19.[5] More neurologists and neuromuscular specialists from across the globe need to submit details of cases to the CARE-MG registry if it is to become more representative—in terms of contributing physicians, patients, and results—and provide the information necessary to enable evidence-based care for patients with myasthenia gravis during this pandemic.

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1 Korsukewitz C, Reddel SW, Bar-Or A, Wiendl H. Neurological immunotherapy in the era of COVID-19—looking for consensus in the literature. *Nat Rev Neurol* 2020; **16:** 493–505.

2 Robberecht W, Bednarik J, Bourgeois P, Van Hees J, Carton H. Myasthenic syndrome caused by direct effect of chloroquine on neuromuscular junction. *Arch Neurol* 1989; **46:** 464–68.

3 Cadisch R, Streit E, Hartmann K. Exacerbation of pseudoparalytic myasthenia gravis following azithromycin (Zithromax). *Schweiz Med Wochenschr* 1996; **126:** 308–10 (in German).

4 Jacob S, Muppidi S, Guidon A, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci* 2020; **412:** 116803.

5 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323:** 1239–42.

6 Myasthenia Gravis Foundation of America. CARE-MG. https://myasthenia.org/For-Professionals/Resources-for-Professionals/CARE-MG (accessed Oct 26, 2020).

Training neurosurgeons in China

In their Correspondence, Norton and colleagues[1] remarked that neurosurgery should be an attractive option for the best medical students, regardless of gender, ethnicity, or socioeconomic status. However, this might not be the case in China. Because of the skills and knowledge that neurosurgical departments demand, recruitment of students is not easy. For example, in some institutions, neurosurgery students had a lower admission score than those in other clinical specialties, such as orthopaedics and cardiology.[2,3] Data from the Beijing Institute of Neurosurgery, Beijing, China, and Department of Neurosurgery, The First Clinical Medicine College, Southern Medical University, Guangzhou, China, also show that many students apply to other departments and switch to neurosurgery only after not being accepted for their first choice. We believe that the long training period, low wages, and heterogeneity of clinical performance across different hospitals might discourage the best candidates from a career in this field.

In 2014, the National Health Commission established standardised training for residents, which extended the training period to 3 years. Standarised 2–4-year training periods for some specialists (eg, 2 years for general surgery and 4 years for neurosurgery) were implemented in 2017.[4,5] All newly licensed doctors who want to specialise in neurosurgery, respiratory and critical care medicine, or cardiology must now complete extended specialist training after finishing their residential training. Although wages for residents have improved, they are still below the average income in other professional fields (eg, ophthalmology).

The heterogeneity in medical standards of neurosurgical departments across China might also pose a problem. In most hospitals, neurosurgeons only manage patients with traumatic brain injury or intracranial haemorrhage, and they do not operate on brain tumours or do endovascular therapy for intracranial aneurysms. The rewards and challenges of complex neurosurgical interventions are restricted to a few hospitals, most of which are located in eastern China.

We encourage every young trainee to try their best for a rewarding neurosurgical career in China. However, solutions to the recruitment and retention of new neurosurgeons are needed.

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1 Norton EJ, Bandyopadhyay S, Moudgil-Joshi J. Social media could address the gender gap in neurosurgery. *Lancet Neurol* 2020; **5:** 382–83.